ABSTRACT

Human diseases caused by dominant, gain-of-function mutations develop in heterozygotes bearing one mutant and one wild-type copy of a gene. Because the wild-type gene often performs important functions, whereas the mutant gene is toxic, any therapeutic strategy must selectively inhibit the mutant while retaining wild-type gene expression. The present invention includes methods of specifically inhibiting the expression of a mutant allele, while preserving the expression of a co-expressed wild-type allele using RNAi, a therapeutic strategy for treating genetic disorders associated with dominant, gain-of-function gene mutations. The invention also includes small interfering RNAs (siRNAs) and small hairpin RNAs (shRNAs) that selectively suppress mutant, but not wild-type, expression of copper zinc superoxide dismutase (SOD1), which causes inherited amyotrophic lateral sclerosis (ALS).